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| EXAMINER | |
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| HILL, KEVIN KAI | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/581,761 | HELLSTROM ET AL. | |
| | Examiner | Art Unit | |
| | KEVIN K. HILL | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 May 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *1-10,12-16 and 18-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,17 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :April 13, 2009, April 20, 2009, July 22, 2009 and March 26, 2010 .

# Detailed Action

## *Election/Restrictions*

Applicant's response to the Requirement for Restriction, filed on May 17, 2010 is acknowledged.

Applicant has elected the invention of Group 11, claim(s) 11, 17 and 21, drawn to a method of affecting vasculogenesis or angiogenesis comprising administering a pharmaceutical composition comprising an isolated polypeptide comprising an amino acid sequence substantially corresponding to one of the SEQ ID NO's recited in Claim 12, wherein vasculogenesis or angiogenesis is **inhibited or decreased**.

Within Group I, Applicant has elected the subgroup g) the amino acid sequence of SEQ ID NO:35 and/or the amino acid sequence of SEQ ID NO:37.

Election of Applicant's invention(s) was made without traverse. The restriction and election requirement is deemed proper and therefore made final (MPEP §818).

Claims 1-10, 12-16 and 18-20 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 11, 17 and 21 are under consideration.

If the claims are amended, added and/or canceled in response to this Office Action, then Applicant is required to follow Amendment Practice under 37 C.F.R. §1.121 AND A CLEAN COPY OF ALL PENDING CLAIMS IS REQUESTED.

1. **Claims 11, 17 and 21 are objected to because of the following informalities**:

This application contains claims drawn to an invention nonelected without traverse in the reply filed on May 17, 2010, whereby the instant claims recite dependency upon non-elected Claims 12 or 16, and the effect of the pharmaceutical compound is to **increase or enhance** vasculogenesis or angiogenesis.

It would be remedial to draft the claims in independent form.

Appropriate correction is required.

## *Priority*

This application is a 371 of PCT/SE04/01814 filed on December 6, 2004.

Acknowledgment is made of Applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). A certified copy of the foreign patent application Sweden 0303268-7 filed on December 5, 2003 is filed with the instant application.

## *Information Disclosure Statement*

Applicant has filed Information Disclosure Statements on April 13, 2009, April 20, 2009, July 22, 2009 and March 26, 2010 that have been considered.

The U.S. Patent application citation on the IDS filed March 26, 2010 is incorrect, and has been lined through. Note that the correct citation is provided in the IDS filed April 20, 2009.

The signed and initialed PTO Forms 1449 are mailed with this action.

## *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

## *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. **Claim 17 is rejected under 35 U.S.C. 101** because the disclosed invention is inoperative and therefore lacks utility. The claim literally recites a method of causing vasculogenesis or angiogenesis **in** [emphasis added] a cell. However, such is physically impossible because those

of ordinary skill in the art immediately recognize that vasculogenesis and angiogenesis are multicellular processes occurring outside a cell.

3. **Claim 17 is rejected under 35 U.S.C. 101** because the claimed invention is not supported by either a credible asserted utility or a well established utility.

4. **Claim 17 is also rejected under 35 U.S.C. 112, first paragraph**. Specifically, since the claimed invention is not supported by either a credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

## *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

5. **Claims 11 and 17 are rejected under 35 U.S.C. 112, second paragraph**, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01.

With respect to Claim 11, the claim literally recites that the pharmaceutical composition causes an increase or decrease in a cell, group of cells or organism. However, the claims are vague and indefinite in that no step(s) in the claimed method(s) refers back to or recapitulates the preamble of the claim. It is unclear how the increase or decrease in a cell, group of cells or organism will achieve the necessary change in vasculogenesis or angiogenesis. The omitted step is a correlation or recapitulation step at the end of the claim which restates the preamble and establishes the necessary nexus between the elements of the claim.

With respect to Claim 17, the claim is self-contradictory. The method is drawn to causing vasculogenesis or angiogenesis by administering a pharmaceutical composition that causes a decrease in vasculogenesis or angiogenesis. The omitted step is a correlation between the

administration of an anti-angiogenic/anti-vasculogenic pharmaceutical to cause vasculogenesis or angiogenesis.

With respect to Claim 17, the claim recites the limitation "the affecting may preferably cause an increase or decrease, more preferably, the cell, group of cells or organism…". Such is unclear because the claim does not recite that which is to be increased or decreased. Does Applicant mean an increase or decrease in the cell, group of cells or organism? If so, then see discussion above per Claim 11. Does Applicant mean an increase or decrease in vasculogenesis or angiogenesis? If so, then see Claim 21 for appropriate language.

With respect to Claim 17, the claim recites the limitation "the affecting" (line 4) in reference to the method's preamble. There is insufficient antecedent basis for this limitation in the claim because "affecting" was cancelled from the claims preamble.

Appropriate correction is required.

## *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. **Claims 11, 17 and 21 are rejected under 35 U.S.C. 103(a)** as being unpatentable over in view of O'Reilly et al (Cell 88:277-285, 1997) in view of Goodwin et al (Angiogenesis 5:109, 2002), Brink et al (WO 97/39357) and Andrews et al (WO 02/077204).

***Determining the scope and contents of the prior art.***

O'Reilly et al teach a method of affecting angiogenesis and/or vasculogenesis in a group of cells or a vertebrate organism, wherein the organism is a mammal, more specifically a mouse model of human cancer, the method comprising administering to said organism a therapeutically effective amount of a pharmaceutical polypeptide agent, Endostatin, whereby vasculogenesis and/or angiogenesis is inhibited or decreased. The organism may be suffering an angiogenesis-related disorder, e.g. cancer. Endostatin is a specific inhibitor of endothelial cell proliferation, is a potent angiogenesis inhibitor, and has strong antitumor activity via suppression of tumor-induced angiogenesis and increased rate of apoptosis (Figure 6). O'Reilly et al contemplate the translation of the method to humans (pg 282, col. 2).

O'Reilly et al do not teach the pharmaceutical polypeptide agent to inhibit or decrease vasculogenesis and/or angiogenesis to be a Wnt-antagonist, e.g. a molecule that competes for Wnt binding. However, at the time of the instantly asserted invention, Goodwin et al taught that Wnt signaling is involved in vasculogenesis and/or angiogenesis, as evidenced by Wnt-2 null mice having abnormal vasculature and reduced capillary phenotypes (pg 3; see reference cited therein) and Fz5 null mice having impaired vascularization phenotypes (pg 4; see reference cited therein). Expression of Wnt-antagonists sFRP1 and FrzB, Frizzled related family members, are

recognized to inhibit vascular Wnt signaling and cause apoptosis. Furthermore, Goodwin et al taught that Wnt signaling was implicated in the mechanism of Endostatin's anti-angiogenic activity, and that inhibition of Wnt by, e.g. increasing the amount of Frizzled related proteins, is expected to result in the regression of vasculature (pgs 6-7; Figure 3).

Neither O'Reilly et al nor Goodwin et al teach the pharmaceutical polypeptide is human or mouse Fz6, or a fragment thereof. However, at the time of the invention, Brink et al disclosed the mouse Fz6 receptor having an amino acid sequence 100% identical to SEQ ID NO:35 (complete search results available in SCORE), and fragments thereof, as well as the ability of the ordinary artisan to use Frizzled receptors, e.g. the cysteine-rich domain (CRD) (pg 4; Example 6).

With respect to SEQ ID NO:37, while Brink et al contemplate human homologs of mouse Fz receptors, Brink et al do not disclose SEQ ID NO:37 which encodes the human homolog of mouse Fz6. However, at the time of the instantly asserted invention, Andrews et al disclosed the amino acid sequence of human Fz6, wherein said amino acid sequence is 99.9% identical (only one amino acid difference; complete search results available in SCORE) to SEQ ID NO:37. Andrews et al disclose that Wnt signaling may be antagonized by molecules that compete for Wnt binding, e.g. Frizzled related proteins, Wnt-inhibitory factors, or active binding fragments of…sFRP-1 (aka FrzA) Fz6 (pg 4; pg 11). Andrews et al contemplate analogues and fragments of full-length Wnt receptors (pg 8).

***Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.***

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in molecular biology, signal transduction and vascular biology. Therefore, the level of ordinary skill in this art is high.

"A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton." *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1397

(2007). "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.* Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at ___, 82 USPQ2d at 1396.

***Considering objective evidence present in the application indicating obviousness or nonobviousness.***

Applicant's working example (pgs 27-28) discloses that inactivation or impairment of the Fz6 receptor results in angiopathy in some of the vertebrates treated with a morpholino gene-silencing molecule. However, the art had previously recognized that inactivation or impairment of Wnt signaling, e.g. via Fz5 receptor or Wnt-2, results in angiopathy in vertebrates (Goodwin et al, pgs 3-4; see references cited therein).

It would have been obvious to one of ordinary skill in the art to try substituting a first Wnt antagonist as taught by O'Reilly et al with a second Wnt antagonist molecule comprising active binding fragments of the Frizzled family, more specifically Fz6 (SEQ ID NO:35 or SEQ ID NO:37) as taught by Brink et al and Andrews et al in view of Goodwin et al in a method of affecting vasculogenesis or angiogenesis in group of cells or an organism, whereby the pharmaceutical agent inhibits or decreases vasculogenesis and/or angiogenesis with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention and "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipate success, it is likely that product not of innovation but of ordinary skill and common sense.". M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)." "Reading a list and selecting a known compound to meet known requirements is no more ingenious than selecting the last piece to put in the last opening in a jig-saw puzzle." 325 U.S. at 335, 65 USPQ at 301.)." When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ

532 (CCPA 1982). M.P.E.P. §2144.06. An artisan would be motivated to try substituting a first Wnt antagonist with a second Wnt antagonist comprising active binding fragments of the Frizzled family, more specifically Fz6 (SEQ ID NO:35 or SEQ ID NO:37) because those of ordinary skill in the art recognized that Wnt signaling may be antagonized by increasing the amount of a Wnt antagonist comprising active binding fragments of the Frizzled family (Goodwin et al, Brink et al, Andrews et al) or by decreasing β-catenin activity (via Endostatin) (O'Reilly et al, Goodwin et al), each Frizzled family member possesses a Wnt-binding motif, i.e. the CRD motif, and there is but a finite number of immediately identified, predictable variants of Wnt-inhibitory molecule comprising active binding fragments of the Frizzled family (Goodwin et al, Brink et al, Andrews et al).

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

## *Conclusion*

7. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to KEVIN K. HILL whose telephone number is (571)272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill/
Primary Examiner, Art Unit 1633